



TFEB in cardiac stress adaptation: more than just lysosomes

Yohan Santin¹ , Jeanne Mialet-Perez²

Citation: Santin Y, Mialet-Perez J. TFEB in cardiac stress adaptation: more than just lysosomes. *J Cardiovasc Aging*. 2026;6:48. <https://dx.doi.org/10.20517/jca.2026.107>

Received: 21 Jul 2026

Accepted: 25 Aug 2026

Published: 15 Oct 2026

Academic Editor:

Houza Chen

Copy Editor:

Ping Zhang

Production Editor:

Ping Zhang

UNCOVERING THE ROLE OF LYSOSOMES IN THE HEART

The remarkable ability of the heart to maintain cellular homeostasis throughout life relies on efficient quality control mechanisms, in which lysosomes play a central role by ensuring the degradation and recycling of cellular components^[1]. These processes become critical during pathological stress, when a sustained increase in workload triggers cardiomyocyte hypertrophy and imposes major demands on cellular quality control and metabolic systems^[2]. Beyond their traditional degradative function, lysosomes have emerged as dynamic signaling and metabolic hubs that coordinate multiple cellular stress responses^[3]. Understanding how lysosome-centered networks contribute to cardiac adaptation may therefore provide new insights into the transition from hypertrophy to heart failure (HF).

TRANSCRIPTION FACTOR EB AS KEY PLAYER

A major regulator of lysosomal function is the basic helix-loop-helix leucine zipper transcription factor EB (TFEB) that belongs to the family of the microphthalmia/transcription factor E^[4]. TFEB activity is regulated by its abundance, its shuttling to the nucleus, and its capacity to bind to the promoters of target genes. Being highly sensitive to nutritional status and organelle damage, TFEB regulates important functions such as lysosomal biogenesis, autophagy, and exocytosis.

ROLE OF TFEB IN CARDIAC DISEASES

Early studies investigating TFEB's role in the heart employed overexpression strategies to restore its function, as TFEB protein expression and/or nuclear translocation were impaired in various stress models. Through gene-targeted therapy, increasing TFEB expression in the heart protected against cardiac injury by improving lysosomal function and autophagic flux in amyloid light-chain (AL) amyloidosis, oxidative stress, and doxorubicin cardiotoxicity^[5-7]. While these studies demonstrated a beneficial role of cardiac TFEB overexpression, conflicting results



¹Univ Toulouse, Inserm, The Institute of Metabolic and Cardiovascular Diseases (I2MC), Toulouse 31000, France.

²Univ Angers, National Institute of Health and Medical Research (INSERM), French National Center for Scientific Research (CNRS), Laboratory for Cardiovascular and mitochondria research (MITOVASC), Federative Research Structure "Cellular Interactions and Therapeutic Applications" (SFR ICAT), Angers 49000, France.

Correspondence to: Dr. Jeanne Mialet-Perez, Univ Angers, National Institute of Health and Medical Research (INSERM), French National Center for Scientific Research (CNRS), Laboratory for Cardiovascular and mitochondria research (MITOVASC), Federative Research Structure "Cellular Interactions and Therapeutic Applications" (SFR ICAT), Angers 49000, France. E-mail: jeanne.perez@inserm.fr

were later obtained in the context of pressure overload. Whereas moderate TFEB overexpression ($\approx$ 2-fold) was protective, high overexpression ($\approx$ 8-fold) was deleterious during the transition from hypertrophy to HF^[8,9]. Excessive and uncontrolled autophagy activation or non-canonical TFEB function might underlie the detrimental cardiac effects observed with high TFEB overexpression^[8]. These findings highlight the importance of finely tuned TFEB activity. However, all studies relied on gain-of-function approaches, leaving the endogenous role of TFEB in the stressed heart unexplored.

BEYOND LYSOSOMES: TFEB AS A CARDIOPROTECTIVE ACTOR THROUGH THE REGULATION OF MITOCHONDRIAL METABOLISM

The new study published in *Circulation Research* by Daou *et al.* employed, for the first time, a cardiomyocyte-specific TFEB knockout mouse model (CTKO) to study pressure overload-induced HF^[10]. Contrary to previous studies, the authors found that TFEB expression was transiently upregulated in the early stages of cardiac hypertrophy. In CTKO mice, transverse aortic constriction (TAC) surgery led to exaggerated hypertrophic growth, rapid transition to HF, and increased mortality compared to wild-type (WT) mice. As expected, CTKO mice failed to increase the expression of lysosomal markers in response to TAC, leading to an accumulation of LC3-II and ubiquitinated proteins, which confirms the importance of TFEB in coordinating the autophagy-lysosome pathway and proteotoxic stress. Having observed blunted phosphorylation of AMP-activated protein kinase alpha (AMPK α) in CTKO mice, Daou *et al.* showed that metformin, an activator of AMPK α , prevented excessive hypertrophy in TAC mice but failed to rescue lysosomal deficiency or ventricular dysfunction^[10]. To investigate the mechanisms linking TFEB deletion to ventricular dysfunction, the authors performed proteomic and transcriptomic analyses in CTKO TAC hearts. Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α), the master regulator of mitochondrial biogenesis and energy metabolism, was markedly downregulated, together with broad alterations in mitochondrial gene programs and function.

DISCUSSION AND PERSPECTIVES

This study by Daou *et al.* provides important insights into how TFEB coordinates the cardiac response to hypertrophic stress^[10]. Their findings support a model in which TFEB engages distinct but interconnected adaptive programs: lysosomal capacity and AMP-activated protein kinase (AMPK) signaling restrain hypertrophic growth, whereas mitochondrial metabolism sustains cardiac function [Figure 1].

The authors identified a previously unrecognized TFEB-AMPK axis, opening an interesting mechanistic avenue. While AMPK is known as a regulator of TFEB activity through a phosphorylation-dependent mechanism^[4], the present study suggests a reciprocal relationship, as TFEB deletion markedly reduced AMPK α phosphorylation in TAC hearts. However, whether lysosomal dysfunction contributes to blunted AMPK activation in CTKO hearts remains to be determined, as does the potential involvement of additional AMPK-independent mechanisms in restraining hypertrophic growth. Indeed, the rescue achieved with metformin supports a role for AMPK in limiting hypertrophy, while its pleiotropic actions leave room for additional pathways linking TFEB/lysosome to metabolic adaptation and cardiac stress response^[11]. For example, whether metformin modulates mitochondrial biogenesis and function in CTKO TFEB hearts after TAC has not been evaluated in the present study.

Another important discovery is that TFEB regulates mitochondrial function. Previous studies demonstrated direct transcriptional control of PGC-1 α by TFEB^[12], and Daou *et al.* identified selective regulation of the PGC-1 α -b isoform, supporting a direct TFEB-driven mitochondrial program^[10]. Alternatively, enhanced

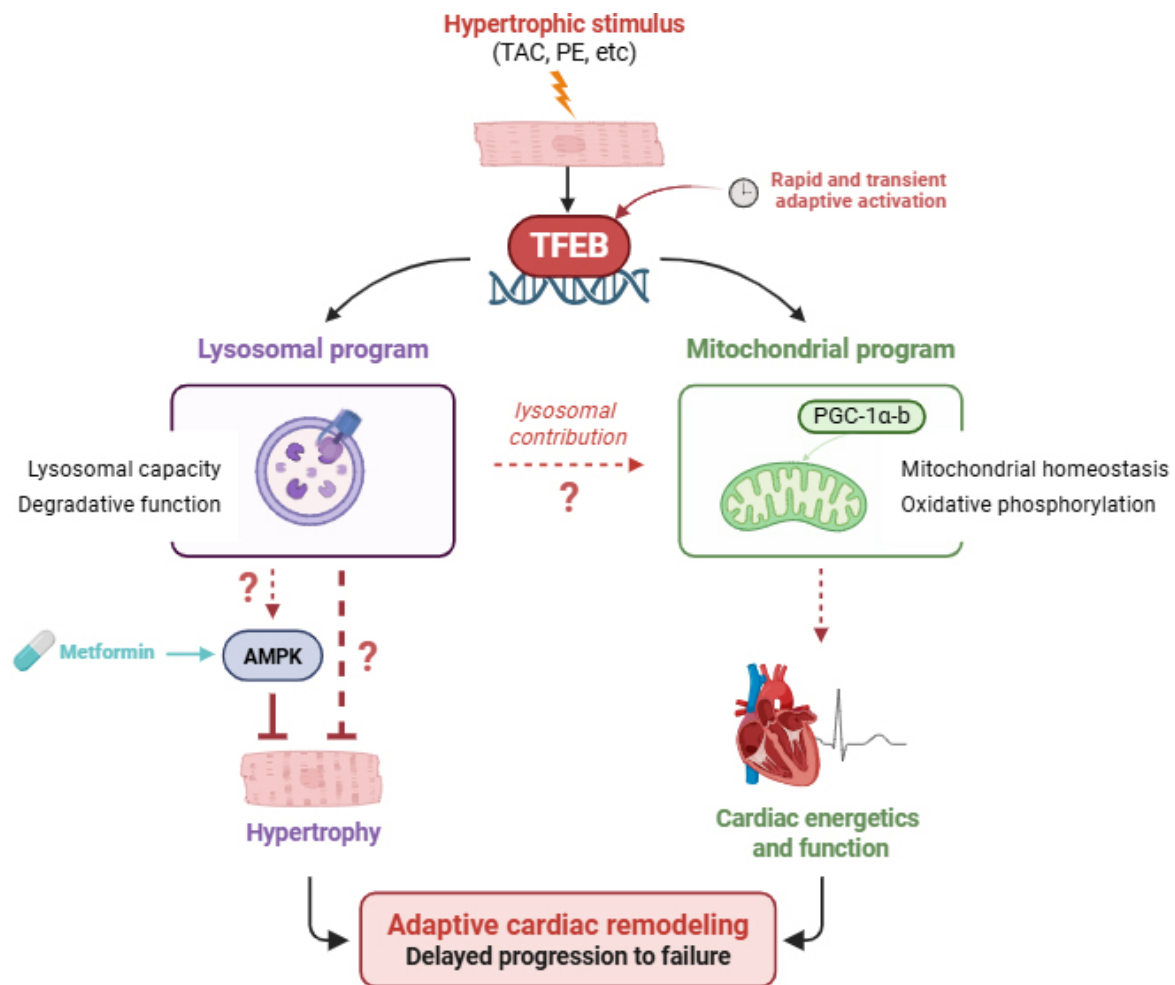


Figure 1. TFEB-mediated adaptation to hypertrophic stress. In response to hypertrophic stimuli, cardiomyocyte TFEB coordinates lysosomal and mitochondrial programs that contribute to limiting hypertrophic growth and preserving cardiac energetics and function. Dashed lines and question marks indicate potential mechanistic links between lysosomal function, AMPK signaling, mitochondrial homeostasis, and cardiac adaptation that remain unresolved and warrant further investigation. Created in BioRender. Santin Y (2026) <https://BioRender.com/t8m2g29>. TFEB: Transcription factor EB; TAC: transverse aortic constriction; PE: phenylephrine; AMPK: AMP-activated protein kinase; PGC-1 α -b: peroxisome proliferator-activated receptor gamma coactivator 1-alpha-b.

lysosomal function may preserve mitochondrial homeostasis by promoting autophagy/mitophagy and mitochondrial quality control^[13]. These mechanisms, however, are not mutually exclusive and may act in concert to preserve mitochondrial function. One way to disentangle their respective contributions would be to improve lysosomal function independently of TFEB. Lysosome-acidifying nanoparticles, which directly restore lysosomal function and improve mitochondrial homeostasis^[14], provide one example of such an approach. Comparing TFEB-independent lysosomal rescue with direct TFEB activation could therefore help define the relative contributions of lysosome-mediated and direct transcriptional mechanisms to mitochondrial protection.

Overall, these findings position TFEB as a compelling therapeutic target at the crossroads of several major adaptive pathways in the heart. By coordinating lysosomal, metabolic, and mitochondrial adaptation, TFEB offers the possibility of simultaneously enhancing multiple aspects of cardiac stress resilience. The growing repertoire of pharmacological strategies capable of enhancing TFEB activity, including natural compounds^[15,16], cardiac glycosides^[17], and synthetic small molecules^[18], further strengthens its translational potential. However, TFEB activation must be finely tuned, as excessive overexpression can be detrimental.

The magnitude, duration, and cellular context of TFEB may ultimately shape the adaptive programs engaged, emphasizing the need to tailor TFEB-targeting strategies to distinct pathological settings.

DECLARATIONS

Authors' contributions

Made substantial contributions to conceptualization, supervision, writing - review and editing: Santin Y, Mialet-Perez J

Availability of data and materials

Not applicable.

AI and AI-assisted tools statement

Not applicable.

Financial support and sponsorship

This work was supported by the MITOCARD grant (Région Pays de la Loire, Angers-Loire Metropole and University of Angers).

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Copyright

© The Author(s) 2026

REFERENCES

1. Henning RH, Brundel BJM. Proteostasis in cardiac health and disease. *Nat Rev Cardiol.* 2017;14:637-53. [DOI PubMed](#)
2. Nakamura M, Sadoshima J. Mechanisms of physiological and pathological cardiac hypertrophy. *Nat Rev Cardiol.* 2018;15:387-407. [DOI PubMed](#)
3. Settembre C, Perera RM. Lysosomes as coordinators of cellular catabolism, metabolic signalling and organ physiology. *Nat Rev Mol Cell Biol.* 2024;25:223-45. [DOI PubMed](#)
4. Takla M, Keshri S, Rubinsztein DC. The post-translational regulation of transcription factor EB (TFEB) in health and disease. *EMBO Rep.* 2023;24:e57574. [DOI PubMed PMC](#)
5. Guan J, Mishra S, Qiu Y, et al. Lysosomal dysfunction and impaired autophagy underlie the pathogenesis of amyloidogenic light chain-mediated cardiotoxicity. *EMBO Mol Med.* 2014;6:1493-507. [DOI PubMed](#)
6. Santin Y, Sicard P, Vigneron F, et al. Oxidative stress by monoamine oxidase-a impairs transcription factor EB activation and autophagosome clearance, leading to cardiomyocyte necrosis and heart failure. *Antioxid Redox Signal.* 2016;25:10-27. [DOI](#)
7. Bartlett JJ, Trivedi PC, Yeung P, Kienesberger PC, Pulinkunnil T. Doxorubicin impairs cardiomyocyte viability by suppressing transcription factor EB expression and disrupting autophagy. *Biochem J.* 2016;473:3769-89. [DOI PubMed](#)
8. Song R, Lei H, Feng L, et al. TFEB insufficiency promotes cardiac hypertrophy by blocking autophagic degradation of GATA4. *J Biol Chem.* 2021;297:101189. [DOI PubMed PMC](#)
9. Wundersitz S, Pablo Tortola C, Schmidt S, et al. The transcription factor EB (TFEB) sensitizes the heart to chronic pressure overload. *Int J Mol Sci.* 2022;23:5943. [DOI PubMed PMC](#)
10. Daou D, Das Gupta S, Anand A, et al. TFEB antagonizes cardiac hypertrophy and failure by enhancing lysosomal capacity and mitochondrial function. *Circ Res.* 2026;139:e328083. [DOI PubMed PMC](#)
11. Foretz M, Guigas B, Viollet B. Metformin: update on mechanisms of action and repurposing potential. *Nat Rev Endocrinol.* 2023;19:460-76. [DOI PubMed PMC](#)

12. Settembre C, De Cegli R, Mansueto G, et al. TFEB controls cellular lipid metabolism through a starvation-induced autoregulatory loop. *Nat Cell Biol*. 2013;15:647-58. [DOI PubMed PMC](#)
13. Ravindran R, Gustafsson ÅB. Mitochondrial quality control in cardiomyocytes: safeguarding the heart against disease and ageing. *Nat Rev Cardiol*. 2025;22:798-813. [DOI PubMed](#)
14. Santin Y, Formoso K, Haidar F, et al. Inhalation of acidic nanoparticles prevents doxorubicin cardiotoxicity through improvement of lysosomal function. *Theranostics*. 2023;13:5435-51. [DOI PubMed PMC](#)
15. Miceli C, Santin Y, Manzella N, et al. Oleuropein aglycone protects against MAO-A-induced autophagy impairment and cardiomyocyte death through activation of TFEB. *Oxid Med Cell Longev*. 2018;2018:8067592. [DOI PubMed](#)
16. Jeong SJ, Stitham J, Evans TD, et al. Trehalose causes low-grade lysosomal stress to activate TFEB and the autophagy-lysosome biogenesis response. *Autophagy*. 2021;17:3740-52. [DOI PubMed PMC](#)
17. Wang C, Niederstrasser H, Douglas PM, et al. Small-molecule TFEB pathway agonists that ameliorate metabolic syndrome in mice and extend *C. elegans* lifespan. *Nat Commun*. 2017;8:2270. [DOI PubMed PMC](#)
18. Chung CY, Shin HR, Berdan CA, et al. Covalent targeting of the vacuolar H⁺-ATPase activates autophagy via mTORC1 inhibition. *Nat Chem Biol*. 2019;15:776-85. [DOI PubMed PMC](#)

Disclaimer/Publisher's Note: All statements, opinions, and data contained in this publication are solely those of the individual author(s) and contributor(s) and do not necessarily reflect those of OAE and/or the editor(s). OAE and/or the editor(s) disclaim any responsibility for harm to persons or property resulting from the use of any ideas, methods, instructions, or products mentioned in the content.



© The Author(s) 2026. Open Access This article is licensed under a Creative Commons Attribution 4.0 International License (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, sharing, adaptation, distribution and reproduction in any medium or format, for any purpose, even commercially, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.